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Oral-appliance therapy obstructive sleep apnea-hypopnea syndrome

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Chapter 7

General discussion

In the treatment of the obstructive sleep apnea-hypopnea syndrome (OSAHS) oral-appliance therapy has emerged as an increasingly popular alternative to continuous positive airway pressure (CPAP). The general aim of this thesis was to evaluate the specific role of oral-appliance therapy in the treatment of OSAHS patients. The merits and shortcomings of the studies in this thesis have already been discussed in detail in the previous chapters. In this chapter the main research outcomes are discussed in a broader context and general conclusions are drawn. Furthermore, this chapter will discuss and suggest aspects that may be considered for future research in oral-appliance therapy for OSAHS.

OSAHS management

Treatment of OSAHS should be aimed primarily at preventing upper airway obstructions during sleep. Probably the most effective approaches are either to pneumatically splint the entire airway, as is achieved with CPAP, or to bypass the upper airway altogether by a tracheotomy. Surgical treatments involve localized amelioration of upper airway patency through the excision of redundant soft tissues or alteration of skeletal structures. The potential for oral appliances to positively impact on airway anatomy is by altering the position of soft tissue and skeletal structures, and possibly by influencing neuromuscular function. Potential advantages over other forms of therapy are their ease of use, reversibility, portability, lack of noise, no power source required, and potentially lower costs. Because there is insufficient scientific evidence for the implementation of oral-appliance therapy as primary treatment in OSAHS, CPAP is currently regarded the evidence-based standard (Chapter 2.1). However, as CPAP therapy requires wearing an obtrusive device, patients may abandon or adhere poorly to therapy. This is especially the case in milder and asymptomatic manifestations of OSAHS. In this respect oral appliances may serve as an adequate treatment alternative.

Based on the systematic review of the available literature regarding the efficacy and co-morbidity of oral-appliance therapy for OSAHS, we concluded that oral appliances are a viable treatment modality for adult OSAHS patients (Chapter 2.2). More recent publications provide additional insight in this matter. Several studies that compared the effects of an oral appliance with an inactive control device found that oral-appliance therapy is clearly more effective in improving the apnea-hypopnea index (AHI), blood pressure, and other physiological outcomes.[1-4] Variable results are, however, reported in improvements of patient-symptomatology including sleepiness and snoring. This has been attributed to factors other than mandibular advancement, such as stimulation of neuromuscular reflexes and changes in the bite relationship, in both oral-appliance and control therapy.[5] However, a recent study that used a placebo tablet instead of an inactive control device also demonstrated improvements of patient-symptomatology following control therapy.[6] These results indicate an important placebo effect when treating OSAHS patients with oral appliances.

Studies on the outcomes of the variability in mandibular advancement and bite-opening (Chapter 2.2) suggest that a mandibular repositioning appliance (MRA) derives its therapeutic effect mainly from the amount of mandibular advancement imposed by the appliance. A recently published controlled study confirms this suggestion.[7] The fact that in some OSAHS patients the number of upper airway obstructions increases when the mandible is protruded towards its maximum still remains.[8] Recent studies have reported on the feasibility of a single night titration of an MRA using remotely controlled appliances.[9,10] This technique may offer the advantage of directly ascertaining the likelihood of treatment success as well as the amount of mandibular advancement required in an individual patient. However, the difficulty of achieving the required mandibular advancement without discomfort on the first night and the laborious character may limit wide scale applications of this technique. Therefore, in clinical practice determination of the amount of mandibular advancement required to prevent OSAHS in a particular patient largely remains a matter of trial and error.

Our findings suggest that, although MRA therapy proved superior to other types of oral appliances, the design (i.e., one-piece or two-piece appliances) has no serious consequences on physiological outcomes in OSAHS management (Chapter 2.2). This suggestion is confirmed by a recent study that also indicated similar effects of different types of MRA's on physiological outcomes.[11] However, in another recently published study it was shown that a prefabricated MRA is generally not as effective as a custom-made one in improving physiological outcomes in OSAHS patients.[12] It appears that, despite the considerable variations in MRA design, physiological effects of different types of custom-made oral appliances that reposition the mandible are remarkably consistent. Appliance design may, however, influence therapeutic efficacy by affecting the patient's preference or subjective outcomes.[1] The precise benefits of specific features in MRA design, especially adjustability in mandibular advancement and freedom of mandibular movement, need to be further elucidated.

When treating patients with mild to moderate OSAHS, oral-appliance therapy is more effective than uvulopalatopharyngoplasty (UPPP) (Chapter 2.2). Although success rates of both treatments showed a tendency to decrease, oral-appliance therapy remains more successful than a UPPP after a four-year treatment period.[13] However, the number of drop-outs in the oral-appliance group at the four-year follow-up examination limits the implications of the results from this study. To date no other surgical interventions have been compared with oral-appliance therapy in the treatment of OSAHS. This unexplored aspect in oral-appliance therapy, therefore, warrants further study.

Six studies included in our systematic review (Chapter 2.2) and one recent publication compared the effects of CPAP with oral-appliance therapy in the treatment of OSAHS.[6] Results from these crossover trials indicate that, when considering physiological outcomes like the AHI, CPAP should be preferred to oral-appliance therapy. Most of these trials did not observe significant differences in subjective parameters, including the Epworth sleepiness scale, when comparing oral-appliance and CPAP therapy. Moreover, changes in sleep quality, such as the amount of rapid-eye-movement (REM) and slow-wave sleep (*i.e.*, non-REM stage 3 and 4), do not differ between these treatments. Some authors propose oral-appliance therapy as a first-line alternative to CPAP in patients with mild to moderate OSAHS,[14,15] whereas others obtain superior results with CPAP in this respect.[16,17] In most studies, however, patients have a clear preference for oral-appliance instead of CPAP therapy.[1,6] These results indicate that CPAP is not an ideal therapy and that in part of the patients oral appliances should be considered alongside CPAP therapy.

In evaluating studies related to the efficacy of oral-appliance therapy one important aspect requires consideration. The overall success rate of oral-appliance therapy in OSAHS patients is reported variably and may range from 15 to 88%.[1,18,19] Factors including the amount of mandibular advancement and the inclusion of OSAHS patients of different disease severity may account for this variation in success. Another factor is that various definitions for treatment success are being used. In OSAHS patients oral-appliance therapy should be aimed at accomplishing a resolution of symptoms, and a normalization of the AHI (*i.e.*, <5) and oxyhemoglobin saturation.[20] In order to compare different studies, a uniform definition for treatment success is clearly necessary. In Chapter 2.2, such a definition for treatment success was suggested which may be practical in both clinical and research situations.

Systematic review of the available literature demonstrated that long-term adverse effects of oral-appliance therapy on the craniomandibular complex are generally limited, whereas orthodontic effects on teeth and dentofacial skeleton are observed more frequently (Chapter 2.2). Our findings suggested that a decreased dental overbite and overjet accompanied by a forward shift of the mandibular first molars relative to the maxillary first molars most likely occurs with long-term oral-appliance therapy. These changes in the dental occlusion may be accompanied by a more lingual inclination of the maxillary incisors and a more labial inclination of the mandibular incisors. Recent (uncontrolled) studies confirm these findings by demonstrating a similar pattern of side-effects with oral-appliance therapy.[21-24]

However, these observations still require confirmation by additional controlled studies.

It appears that dental and skeletal changes with oral-appliance therapy may progress and become more prominent over time.[21,25-27] Skeletal changes, which most likely relate to repositioning of the mandibular condyles, have been demonstrated to occur soon after the onset of treatment whereas changes in the dental occlusion may develop as treatment continues.[27] Recent studies suggest that the occurrence of dental side-effects may be predicted based on initial characteristics in dental occlusion or dentofacial pattern. A small reduction of the dental overjet has been associated with an initially large overbite and small overjet.[24,28] Changes in dental occlusion following long-term oral appliance use have also been classified as "favorable" and "unfavorable".[24] In the latter study, 44% of the patients were deemed to have unfavorable dental changes after an average of 7.4 years of therapy. The "favorable" dental changes were mostly seen in patients with greater initial overbites and mandibular deficiencies. The question to what extent other aspects, such as the specific design of the appliance, periodontal health, patient compliance and the amount of mandibular protrusion, affect the frequency and severity of side-effects with oral-appliance therapy remains to be answered.[1,21,25,28,29] Although it appears that adverse effects of oral-appliance therapy generally involve changes in the dental occlusion, controlled studies are warranted that should address the specific effects of oral-appliance therapy, and related aspects, on the occurrence and progression of adverse effects.

Oral appliances versus CPAP

The concept that CPAP therapy should be used as a first-line treatment in all OSAHS patients is increasingly abandoned. Comparative and preferably randomized studies offer the best means to find out whether an alternative treatment is competitive to CPAP. In the case of oral appliances, seven studies have been published that compared the effects of CPAP with oral-appliance therapy for the treatment of OSAHS.[1,6] All studies used a crossover design and were generally limited to polysomnographic and (elementary) neurobehavioral outcomes. Despite the quantity of studies comparing oral-appliance and CPAP therapy, the specific indications for oral-appliance therapy remained indeterminate. In addition, details on the exact effects of oral-appliance relative to CPAP therapy on secondary outcomes like cardiac function are largely unknown. To further explore the specific role for oral appliances in the treatment of OSAHS, we performed a randomized parallel trial (Chapter 4 and 5).

Our primary aim was to establish specific indications for using oral appliances (Chapter 4.1). We observed that oral-appliance therapy is not inferior to CPAP in the effective treatment of OSAHS. Although both therapies produced substantial improvements in most polysomnographic and neurobehavioral outcomes, CPAP was more effective in improving the AHI and was superior to oral-appliance therapy for patients with severe OSAHS. A more pronounced effect of CPAP on the AHI concurs with most previous studies comparing oral-appliance and CPAP therapy.[1,6] Unlike most previous studies we also included OSAHS patients with severe disease. Therefore, our study covers the entire spectrum of disease. In addition, our results show a more positive effect of oral-appliance therapy than in previous studies. Although many factors may explain this phenomenon, it most likely relates to the greater mandibular advancement with oral-appliance therapy in our study. These findings underline the suggestion that an MRA derives its therapeutic effect mainly from the amount of mandibular advancement imposed by the appliance.

With respect to the specific indications, our findings suggest that oral appliances should be considered, alongside CPAP therapy, as treatment for patients with mild to moderate OSAHS. Among patients with severe disease, oral-appliance therapy should be considered for patients unwilling or unable to tolerate CPAP. These findings correspond with recently introduced practice parameters of the American Sleep Disorders Association.[20] According to these practice parameters, oral-appliance therapy should be considered in patients with mild to moderate OSAHS who prefer this treatment to CPAP, or in patients who fail treatment attempts with CPAP or conservative measures. Because in severe OSAHS oral appliances are generally not as effective as CPAP therapy, these patients should always have an initial trial with CPAP. In patients with severe OSAHS, oral appliances are recommended when CPAP therapy is not tolerated or refused, and when patients are no candidate for or refuse upper airway surgery (*e.g.*, maxillomandibular advancement surgery). Follow-up studies on the effectiveness and adverse effects of oral-appliance and CPAP therapy should be performed to show if these recommendations also hold for the long-term.

Contrary to the specific indication for oral appliances, the effects of therapy on simulated driving performance and cardiac function were less distinct. As observed in previous studies, we found that untreated OSAHS patients perform worse on a simulated driving test when compared with control subjects (Chapter 4.2). Our findings also suggest that effective OSAHS treatment, with either oral-appliance or CPAP therapy, contributes to an improvement of simulated driving performance. However, conclusions beyond both treatments improving simulated driving performance were not justified by our study data. When evaluating the effects of oral-appliance therapy on cardiac function, we demonstrated that patients with moderate to severe OSAHS without established cardiovascular disease often have abnormal left ventricular structure and elevated natriuretic peptides (Chapter 4.3).

These patients, therefore, appear at increased risk of developing cardiovascular disease. Significant changes in natriuretic peptide values indicate an improvement of cardiac function following effective oral-appliance therapy. By evaluating the effects of oral-appliance and CPAP therapy on simulated driving performance and cardiac function in, otherwise healthy, OSAHS patients a relatively unexplored aspect in oral-appliance therapy was studied. However, the conclusions from these studies were limited primarily by the relatively small study populations. Both studies were of an explorative character and not based on a power calculation. Therefore, studies with larger sample sizes are warranted to elucidate the specific differences in effects of oral-appliance and CPAP therapy on simulated driving performance and cardiac function.

We demonstrated that OSAHS patients show more sexual dysfunction compared with aged matched control subjects (Chapter 4.4). Sexual dysfunction in OSAHS patients appears to be related primarily to erectile dysfunction; however, it may also involve complaints of sexual dissatisfaction. Significant improvements of sexual functioning in either the oral-appliance or CPAP treated group could not be established in our study. Because our findings did suggest that patients with pronounced complaints of erectile dysfunction experience some improvement following OSAHS treatment, studies on the effects of oral-appliance and CPAP therapy in patients suffering from sexual dysfunction are of interest.

Some general methodological aspects regarding the studies presented in Chapter 4 require some further consideration. In line with the limited patient sample in the studies evaluating the effects of therapy on simulated driving performance and cardiac function is the fact that randomization resulted in dissimilar baseline characteristics in the treatment groups (Chapter 4.2 and 4.3). Although both studies provide insight in new aspects of oral-appliance therapy, dissimilarities in baseline characteristics impede a reliable comparison of the therapeutic effect of oral-appliance and CPAP therapy. A second consideration is that a placebo effect may account for some changes in neurobehavioral outcomes (Chapter 4.1), simulated driving performance (Chapter 4.2) and sexual function (Chapter 4.4). Placebo controlled studies with respect to CPAP therapy suggest a limited effect of placebo therapy in improvements of simulated driving performance.[30] Moreover, a placebo effect has been demonstrated to affect the outcome of oral-appliance and CPAP therapy to a similar extent.[6] Therefore, the precise value of a placebo intervention in our randomized study would have been questionable.

It may be argued that the method of CPAP-titration (*i.e.*, Nap-titration) performed in the present work is not likely to be optimal with regard to measure optimal conditions for effectiveness of CPAP therapy (Chapter 3). Because in our hospital setting polysomnography is conducted on an ambulatory basis, manual CPAP-titration was not feasible. Following Nap-titration of CPAP, the improvements in AHI and other polysomnographic outcomes were, however, consistent with results from other studies that evaluated the effects of manual CPAP titration.[31-33] Moreover, despite the fact that manual CPAP-titration is considered the "reference standard", guidelines for this procedure are undefined and its reproducibility is not well known.[34] By aiming for an AHI <5 with Nap-titration, we conformed to a generally accepted criterion for optimal CPAP efficacy.[35] Therefore, despite the lack of manual titration as "reference standard", the present titration technique was contrasted to a valid standard. Consequently we consider the means of CPAP-titration performed in the present work an appropriate procedure for the adequate implementation of CPAP in both a clinical situation and for research purposes.

In addition to the method of CPAP-titration, it could be argued that the definition for treatment effectiveness used in the present work is not compatible with the goals of optimal treatment success in OSAHS therapy (Chapter 4 and 5). Although, treatment was always aimed at attaining an AHI <5, this could not always be accomplished due to limitations in mandibular protrusion with oral-appliance therapy or pressure intolerance with CPAP. Moreover, patients with a suboptimal post-therapeutic AHI (*i.e.*, AHI >5) are not easily motivated to abandon therapy in case their OSAHS related symptoms have improved to the patients' satisfaction. In clinical practice OSAHS management should not only be aimed at treating a laboratory outcome (*i.e.*, the AHI), but also at treating the prime reason for consultation, generally being complaints of excessive sleepiness and snoring. In case an AHI <5 could not be attained we, therefore, considered treatment with either oral-appliance or CPAP therapy effective when patients displayed a partial "laboratory response" to therapy (*i.e*, a reduction in AHI of at least 50% from the baseline value to a value of <20 in a patient who had no symptoms while using therapy). However, when compared with the rigid criterion of AHI <5 for success, the criterion for therapeutic effectiveness used in the present work may well have allowed for a significantly less than optimal potential for effectiveness. Moreover, patients with an AHI ≥5 at follow-up review for whom treatment was nonetheless considered effective had an index in the range of five to 20. It could be argued that these patients may be at risk of having a cardiovascular event. However, recent studies indicate that especially patients with severe OSAHS are at risk of developing various cardiovascular events.[36,37] With respect to the definition for treatment success, these considerations may be additional arguments for only using oral-appliance therapy as a primary treatment in patients with non-severe OSAHS.

A final consideration is that treatment adherence to oral-appliance and CPAP therapy was assessed by self-reports only (Chapter 3 and 4). Whereas CPAP usage can be monitored covertly with a mechanism built into the device, oral-appliance usage cannot be assessed covertly in any reliable way. Although results from the present work suggest similar treatment adherence to both oral-appliance and CPAP therapy, compliance rates have been reported variably in other studies. Some studies did not find any differences between both treatments,[16,38] whereas others suggest superior compliance with oral-appliance therapy.[14,17] Additional studies comparing treatment adherence of oral-appliance and CPAP therapy by means of covert compliance monitoring techniques are clearly indicated.

The results from our randomized trial suggest that oral appliances are primarily indicated in patients with mild to moderate OSAHS (Chapter 4.1). These findings were corroborated in the study on predictors of treatment outcome which demonstrated that severity of disease, as indicated by the AHI, was of predictive value for the outcome of oral-appliance therapy (Chapter 5). Moreover, this study demonstrated that the outcome of oral-appliance therapy appears favorable especially in patients who are less obese and have certain craniofacial characteristics (mandibular retrognatism in particular). While only requiring information on the patient's maximum mandibular advancement, AHI, and intermaxillary and mandibular relationship, the predictive models obtained in this study classified the outcome of oral-appliance therapy correctly in 80% of cases. Conversely, the outcome of CPAP therapy could not be predicted in a reliable way. Although most of the predictive variables may be easily determined in clinical practice, they are not valuable for selecting those patients unlikely to respond to CPAP therapy. Unfortunately, in clinical practice these patients are usually deemed the best candidates for oral-appliance therapy.[4] In patients with mild to moderate OSAHS the predictive variables may, however, be used to preselect those candidates most likely to respond favorable to oral-appliance therapy. Additional studies testing the predictive model in other types of oral appliances may be of value to define if our findings are also applicable to a general clinical situation.

Oral appliances in specific cases

The results from the two studies describing the use of oral appliances in specific cases offer some promising frontiers in the treatment of OSAHS patients. Although maxillomandibular advancement surgery is generally a successful surgical intervention for OSAHS,[39] it is an extensive procedure that results in irreversible alterations of the craniofacial complex. Results from our patient series suggest that in the treatment of OSAHS patients, MRA therapy might be a good predictor for the successful outcome of maxillomandibular advancement surgery (Chapter 6.1). A recent study reported a case in which an OSAHS patient was successfully treated by osseous distraction of the mandible followed by a le Fort I osteotomy of the maxilla.[40] By gradually advancing the mandible with the use of a distraction device, the mandibular elongation required was determined according to clinical criteria and polysomnographic indices. Similarly, because the advancement of the maxillomandibular complex is generally somewhat arbitrarily defined, the degree of mandibular advancement with MRA therapy may be used as an estimate for the amount of mandibular advancement required with maxillomandibular advancement surgery. Additional studies with larger sample sizes should further explore this aspect of the predictive value of MRA therapy for the outcome of maxillomandibular advancement surgery.

When considering oral-appliance therapy several dental exclusion criteria should be taken into account. As suggested in previous studies,[41] we found that in a high percentage of cases (*i.e.*, 25%) oral-appliance therapy could not be initiated due to dental limitations (Chapter 4.1). The main reason for disqualifying patients from oral-appliance therapy is usually an insufficient number of teeth to support and retain the appliance. We demonstrated that the placement of endosseous implants to stabilize and retain an MRA is worth the consideration in edentulous OSAHS patients (Chapter 6.2). However, therapeutic acceptance and the amount of mandibular advancement may be compromised by excessive pressure of the MRA on the labial mucosa in the maxilla. To overcome this limitation we suggest that an implant retained MRA in the maxilla is offered as a secondary treatment in selected patients. Additional studies evaluating the feasibility of this secondary treatment are of interest. Because dental implants in MRA therapy are subjected to a different pattern of loading when compared with implant retained overdentures, these studies should also focus on possible complications in osseointegration and implant survival on the long-term.

Conclusions

The aim of this thesis was to evaluate the specific role of oral-appliance therapy in the treatment of OSAHS patients. Based on our systematic review we conclude that the available literature offers an evidence base for the use of oral appliances in the treatment of, especially mild to moderate, OSAHS patients. Oral appliances are effective in the treatment of OSAHS, although a placebo effect should be considered. In the treatment of OSAHS, MRA therapy generally yields superior results to other types of oral appliances. Therapeutic efficacy in MRA therapy is mainly related to the amount of mandibular advancement imposed by the appliance. Moreover, appliance design like the amount of bite-opening or the means of mandibular fixation may affect subjective parameters of success. Although short-term results indicate that MRA therapy should be preferred to UPPP, definite conclusions cannot be drawn. Superior results with respect to physiological outcomes, such as the AHI, indicate that CPAP should be preferred to MRA therapy. However, a clear patient preference for MRA therapy indicates that CPAP should not be considered ideal in the treatment of all OSAHS patients. MRA therapy may result in adverse, although generally not serious, effects on the craniomandibular and craniofacial complex. Adverse effects on the craniofacial complex are found most often following MRA therapy and generally involve changes in the dental occlusion.

Our randomized parallel trial demonstrated that oral-appliance therapy was not inferior to CPAP as effective treatment of OSAHS. However, subgroup analysis suggested that an oral appliance is particularly indicated for patients with mild to moderate disease. Moreover, the outcome of oral-appliance therapy was favorable especially in less obese patients with more pronounced maximum mandibular advancement and certain craniofacial characteristics (mandibular retrognatism in particular). These variables therefore may be used for preselecting suitable candidates for oral-appliance therapy. Our results also suggest that untreated OSAHS patients perform worse on a simulated driving test when compared with control subjects. Moreover, a substantial proportion of severe OSAHS patients without known cardiac disease display abnormal left ventricular structure and functional cardiac impairment. The effects of oral-appliance and CPAP therapy on simulated driving performance and cardiac function are less distinct. Our findings suggest that OSAHS management with either oral-appliance or CPAP therapy usually results in an improvement of simulated driving performance. Moreover, effective oral-appliance therapy may result in an improvement of functional cardiac impairment. However, implications of these findings are constrained by the relatively small populations studied. Our work confirms that male OSAHS patients show more sexual dysfunctions compared with aged matched control subjects. Although we could not establish significant improvements in sexual functioning in either the oral-appliance or CPAP treated patients, our findings do suggest that untreated patients with pronounced erectile dysfunction experience some improvement following OSAHS treatment. In specific cases oral appliances may be used to predict the outcome of maxillomandibular advancement surgery. Moreover, in selected patients who are edentulous, an implant retained MRA in the mandible may be a viable treatment modality for OSAHS.

After studying the specific role of oral appliances in the treatment of OSAHS patients we conclude that this therapy may be recommended as primary treatment in patients with mild to moderate OSAHS besides CPAP therapy. The evidence supporting oral-appliance therapy for mild to moderate OSAHS is sustained by the fact that cross-over studies have shown that patients generally prefer oral-appliance over CPAP therapy. In severe OSAHS and specific patient populations (*e.g.*, edentulous patients), CPAP therapy should always be considered first whereas oral appliances may be used as a secondary intervention.

Future perspectives

Based on the results obtained from our work and from previous studies,[18-20] oral-appliance therapy should be considered a viable and competitive treatment modality in OSAHS management. Although the specific role for oral-appliances appears to be related primarily to the treatment of patients with mild to moderate OSAHS, there are still several aspects in literature that are either controversial or require further study. Long-term studies should confirm whether oral-appliance therapy may be considered, alongside CPAP therapy, as primary intervention for OSAHS in patients with mild to moderate disease. As is the case with the titration of CPAP therapy, future studies should also focus on predictors or specific techniques for determining the effective amount of mandibular advancement with oral-appliance therapy. At present oral-appliance usage cannot be assessed covertly in any reliable way. In order to compare oral-appliance therapy and CPAP on this aspect, a means of covert compliance monitoring should also be developed for oral appliances. Studies on therapeutic compliance with oral-appliance and CPAP therapy in patients with non-severe disease may further refine the specific indication for oral appliances in OSAHS management. Moreover, specific differences in neurobehavioral and cardiovascular outcomes between oral-appliance and CPAP therapy should be further explored in larger (power analysis based) study populations. Besides CPAP therapy, additional studies evaluating the effectiveness of oral-appliance therapy relative to other treatment modalities are of interest (*e.g.*, surgical interventions). In order to compare different types of interventions a uniform definition of treatment success is clearly indicated.

In patients with mild to moderate OSAHS the predictive variables found in the present thesis may be used to preselect those candidates most likely to respond favorable to oral-appliance therapy. Additional studies testing the predictive models on other types of oral appliances may be of additional value to determine if our findings are also applicable to a general clinical situation. An area of debate remains the precise value of specific features in MRA design. Especially adjustability in mandibular advancement and freedom of mandibular movement are aspects that require further study. It is also a question as to whether the specific design of the appliance, periodontal health, patient compliance and the amount of mandibular protrusion affect the frequency and severity of side-effects with oral-appliance therapy. Although it appears that adverse effects of oral-appliance therapy generally involve changes in dental occlusion, controlled studies are warranted that should address the effects of the factors stated above on therapeutic side-effects. Additional studies should also evaluate the feasibility of an implant retained MRA in the long-term treatment of OSAHS, and should further explore the predictive value of MRA therapy for the outcome of maxillomandibular advancement surgery in larger study populations.

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